Impacts of bicyclo-monoterpene enhancers on transdermal delivery of ligustrazine

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Abstract: The purpose of this study is to investigate the impacts of bicyclo-monoterpene promoters (i.e., borneol and camphor) on the *in vitro* permeation of ligustrazine (LGT) through the hairless porcine dorsal skin. Fourier transform-infrared (FT-IR), scanning electron microscope (SEM) and transdermal delivery kinetics *in vitro* were performed to investigate the effect of the promoters on the biophysical changes to the stratum corneum (SC), the surface changes to porcine skin and the *in vitro* percutaneous fluxes of ligustrazine through procine skin. FT-IR results revealed that the peak shift and the decrease in the peak area with borneol were higher than those with camphor. SEM studies demonstrated that the morphological change to SC was related to the chosen enhancer. It was observed that the SC lipid extraction with borneol and camphor led to disruption of the SC and the scutella desquamation. Apparent density (AD) was utilized to describe the desquamation extent of the scutella. Percutaneous fluxes of ligustrazine through porcine skin were evaluated *in vitro* by the Franz-type diffusion cells. Use of borneol led to greater penetration of ligustrazine across porcine skin. It was shown that the permeation enhancement mechanism of bicyclo-monoterpenes to ligustrazine included extracting and disordering lipids which involved the shift changes in C-H stretching and H-bonding action between enhancers and cermaide. The penetration capability of the hydroxy groups in bicyclo-monoterpenes was better than that of the ketone groups.

Key words: percutaneous absorption; bicyclo-monoterpene enhancer; permeation mechanism; ligustrazine
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双环单萜促透剂对川芎嗪透皮吸收的影响

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摘要: 研究双环单萜促透剂 (冰片与樟脑) 对川芎嗪透皮吸收的影响及其作用机制。分别采用傅里叶红外光谱法、扫描电镜法和体外透皮动力学法研究促透剂对角质层的生物物理变化、猪皮表面的变化及川芎嗪体外透过量的影响, 并采用表观密度评价角质鳞片脱落的程度。红外光谱结果表明, 以冰片为促透剂使角质层脂质中的对称与不对称峰的峰位移及峰面积降低值均高于樟脑; 扫描电镜结果表明, 角质层的形态学变化与采用的促透剂有关, 冰片与樟脑对角质层脂质的抽提作用导致角质层的破裂及角质鳞片的脱落; 川芎嗪的体外透过量结果显示, 以冰片为促透剂的透过量大于樟脑。双环单萜促透剂对川芎嗪的促透机制包括对脂质的抽提和扰动作用, 这些作用与 C-H 伸缩震动的位移变化及促透剂与神经酰胺的氢键作用相关; 双环单萜促透剂 (冰片与樟脑) 中羟基的促透能力较酮基的促透能力强。

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关键词: 透皮吸收; 双环单萜促透剂; 透皮机制; 川芎嗪

Ligustrazine (LGT) is isolated from chuanxiong, a frequently used Chinese herb, and has been used as venous administered formulation to treat cardiovascular and cerebrovascular diseases since 1970s. Due to its short half-life, ligustrazine needs to be administered frequently, resulting in variations in absorption and cumulative toxicosis[1−3]. However, the side effects of LGT could be avoided through transdermal administration. Success of the transdermal route depends on drugs' ability to permeate skin at a rate and in amounts to attain sufficient blood exposure[4]. Without enhancers, the percutaneous flux of LGT led to insufficient plasma concentration.

The principle hindrance to percutaneous absorption is the stratum corneum (SC), the outermost layer of the skin, which is composed of keratin-rich cells embedded in multiple lipid bilayers of ceramides, fatty acids and cholesterol[5, 6]. The main path of most drugs through the SC is considered as through intercellular lipid domain[7, 8]. Therefore, the physical and chemical methods which affect the properties of lipids including free fatty acids, cholesterol and ceramides will play a key role for drug penetration through the SC. Penetration promoters modifying the organization of the intercellular lipids, such as changing lipids fluidity and extracting lipids, are effective and convenient.

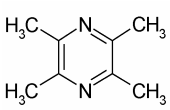
Borneol and camphor are bicyclo-monoterpenes which have low skin irritancy and are good promoters to lipophilic[9, 10] and hydrophilic[11−13] drugs. Borneol differs from camphor only by a hydroxy group at C2 postion instead of a ketone group. Borneol and camphor are chosen to elucidate the difference in permeation activity caused by the hydroxy group and the ketone group.

The interactions between penetration enhancers and lipids or between drugs and lipids can be investigated by fourier transform-infrared (FT-IR) and the morphological changes in the surface of the skin can be observed by scanning electron microscope (SEM). Both are important methods to understand the permeation enhancement mechanism of bicyclo-monoterpenes.

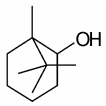
The purpose of this paper is to investigate the permeation mechanism of borneol and camphor on transdermal delivery of LGT, and the relationship between the functional groups of enhancers and the permeation flux of LGT. Apparent density, a new concept, was used to evaluate the morphological differences of the skin treated with different enhancers[14−16].

Materials and methods

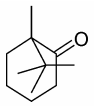
Materials Ligustrazine (Guangdong Songbai Pharmaceutical Corporation), polyvinyl alcohol (PVA, China Pharmaceutical University), sodium carboxymethyl cellulose (CMC-Na, Tianjin Bodi Chemical Company), Azone (Shanghai Qidi Chemical Corporation), DL-borneol (Guangzhou Huangpu Chemical Plant), DL-camphor (Development Perfumery Co. of Jiangxi Shanjiang County) and potassium bromide (Jasco) were used.



Ligustrazine



Borneol



Camphor

Preparation of matrix Film casting technique was used to prepare PVA matrix. 7.0 g of PVA and 3.0 g of CMC-Na were weighed and placed in 150 mL water for swelling overnight, then were dissolved by heating with vigorous stirring. The water solution containing 400 mg ligustrazine was added to the polymeric solution, and was cast onto a glass plate of 400 cm^2 and allowed to dry at room temperature for four days. The entire sheet was cut into small round pieces (radius = 1 cm) and the thickness (0.198 mm ± 0.01 mm), weight (0.17 g ± 0.01 g) and moisture (9.05% ± 0.21%) of each piece were measured accurately. The drug content in the matrix was 1 $mg \cdot cm^{-2}$.

HPLC analysis of samples Samples were analyzed for LGT content using Agilent 1100 series equipped with an auto-sampler, an ultraviolet detector and ODS column (Zorbax, 5 μm, 4 mm × 250 mm, Agilent) at ambient temperature. 20 μL solution from each vial was injected and the quantification of LGT was performed by integration of peaks detected at 294 nm. The mobile phase consisted of methanol and water (6∶4) was a flow rate of 0.8 $mL \cdot min^{-1}$. A calibration curve (peak area *vs* drug concentration) was constructed by running standard LGT (base) solutions in methanol and water (6∶4) for every series of chromatograph samples. Calibration curves were linear over the

range of 0.31−31 μg·mL^{-1}.

Preparation of skin samples for *in vitro* studies Porcine skin was chosen as a model membrane due to its close resemblance to human skin in permeability[17−19]. Porcine weighing 35 kg was purchased from the animal holding unit in Southern Medical University. Hair on the back of porcine skin was carefully removed with electric clipper without damaging the stratum corneum. The hair-free back skin was excised with a pair of scissors and a surgical blade, and the adhesive subcutaneous fat, tissues and capillaries were ablated. 3.14 cm^2 circular skin samples were prepared for permeation studies.

Preparation of SC for FT-IR The SC was obtained from the epidermis by soaking in water at 60 ℃ for 60 s and incubated in a 0.25% trypsin solution at 37 ℃ for 24 h. The SC was washed with ultra-pure water, blotted dry, stored in desiccator at room temperature overnight, then dipped in 3% enhancer ethanols for 6 h and dried for FT-IR. The dehydrated SC treated with no enhancers was used as the control (ethanol solution). The experiment was repeated three times. The FT-IR spectra photographs were generated from a Jasco FT/IR-480 spectrometer and the data were processed using SPSS 10.0.

Preparation of skin for scanning electron microscope Hair, adhesive subcutaneous fat, tissues and capillaries of the porcine skin were removed according to preparation of skin samples for *in vitro* studies. Skins of appropriate sizes (1 cm × 1 cm) were taken and placed in the various 3% enhancer solution for 6 h, washed 6 times with ethanol and stored at 2.5% glutaraldehyde overnight in the freezer. The skin samples were then examined by a scanning electron microscope. The skin without enhancer treatment (ethanol solution) was used as the control. Every experiment was repeated six times and the data were processed with SPSS 10.0.

***In vitro* skin permeation studies** The Franz-type diffusion cells were used for *in vitro* skin penetration studies. 3% enhancers were added onto the stratum corneum of 3.14 cm^2 circular skin samples for 1 h. A PVA film was placed on the pretreated skin sample and mounted between the compartments of the diffusion cells with stratum corneum facing the donor compartment. The temperature of the receptor chambers with physiologic saline were kept at 32 ℃ (shell temperature) and the solution of receptor compartments was stirred continuously at 300 r·min^{-1}. The diffusion surface was 3.14 cm^2. The receiver solution was withdrawn at predetermined time points (1, 2, 3, 4, 6, 8, 10, 12, 14, 18, and 24 h), and replenished with an equivalent volume of saline. The content of ligustrazine in each sample was determined by the previously described HPLC method and reported as average of three measurements.

Data analysis Due to sampling from the receptor compartments and replenishing to them, the receiver solution was constantly being diluted. Therefore, the cumulative permeation (Q_t) of LGT was calculated from the equation: $Q_t = V_r C_t + \sum_{i=0}^{t-1} V_s C_i$

Where C_i was the drug concentration of the receptor solution at each sampling time, C_t was the drug concentration of the sample in the receptor, and V_r and V_s were the volumes of the receiver solution and the sampling solution, respectively. The steady-state fluxes (J_{ss}) could be calculated *via* the equation at steady state: $J_{ss} = \Delta Q_t/(\Delta T \cdot S)$

Apparent permeability coefficients (K_p) were calculated according to the equation: $K_p = J_{ss}/C_d$

Where C_d was the drug content in the matrix (1.0 mg·cm^{-2} × S), while the drug content in the receptor was negligible compared with the drug in the matrix.

Calculation of the apparent density The picture of skin from Hitachi S-3005N SEM was first turned into *tiff* pattern and then analyzed with image tool software. An area in the picture was chosen randomly and the number of desquamation scutella from the skin was counted. The apparent density, which was introduced to describe the quantity of desquamation scutella from skin, was calculated according to the equation: AD = N/A (Where A is the chosen area, N is the number of scutella and AD is the apparent density). At least 6 areas in each image were chosen to calculate the AD. Data was treated with SPSS 10.0.

Results and discussion

1 FT-IR studies

Microscopic studies of FT-IR can reveal the changes in biophysical properties of lipid bilayers by observing absorption peaks of C-H bending and stretching vibration. Moreover, the C-H bending vibration is much weaker than C-H stretching vibration[20]. Thus, the study of lipid biophysical changes was focused on the asymmetric and symmetric C-H stretching absorption appearing near 2 920 cm^{-1} and 2 850 cm^{-1} [21].

The peak shift to higher frequency occurred when CH_2 groups along with the alkyl chain of lipids change from *trans* to gauche conformation[22]. It indicated that the lipid was disordered. The value of the peak shift in C-H stretching vibration was proportional to the ratio of *trans* to gauche conformations in the alkyl chain. Many reports demonstrated that the higher shift of C-H stretching vibration improved drug permeation[23−25], and the decrease in peak areas of the two C-H stretching vibration absorption bands were inversely proportional to the amount of the lipids in SC. In other words, any extraction of the lipids by enhancer, which would result in decrease in peak areas, would be beneficial to drug permeation[26, 27].

Infrared absorption spectra are displayed in Figure 1. Peak shifts of infrared spectra are listed in Table 1. The FT-IR results indicated that C-H stretching vibrations peak generated higher shifts in asymmetric and symmetric positions. The peak shifts with borneol were larger than those with camphor, indicating that the capacity of borneol in disturbing lipid was stronger than that of camphor. The changes in peak areas of C-H stretching vibration are listed in Table 2. The decreases in the peak areas with borneol were higher than those with camphor. Therefore, the extraction activity of borneol was stronger than that of camphor.

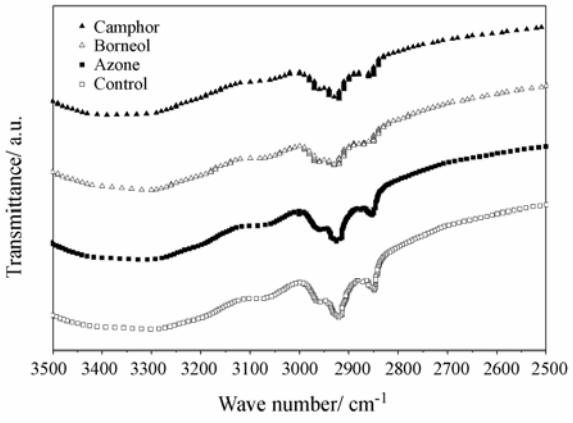


Figure 1 Infrared absorption spectra by different enhancers

For FT-IR spectrum of C-H stretching vibration, the drug has higher permeation fluxes due to the higher peak shift and greater decrease in peak area. The penetration flux of LGT with borneol should be higher than that with camphor. From the results of Table 1, the order of permeation ability to LGT was borneol > camphor > control. Extracting and disturbing lipid mechanisms can explain why the flux by borneol was higher than that by camphor. Therefore, we can conclude that the enhancing mechanisms of borneol and camphor include disturbing and extracting the SC lipids.

2 Scanning electron microscopic study

Microscopic changes in the skin treated with various enhancers were examined by SEM. Figure 2 (a−c) showed the images of the skin surface treated with borneol, camphor and control for 6 h. From Figure 2 (a, b), a large number of scutella were desquamated from the porcine skin treated with the enhancers. In addition, the surface of skin was very plain after the desquamation. Figure 2 (c) showed that there was no desquamated scutella in the intact skin and there were a large number of wrinkles in the

Table 1 Spectral shifts of infrared spectroscopy of porcine stratum corneum (SC). Data were expressed as the $\bar{x} \pm$ SD, n = 3; $^{*}P < 0.05$ *vs* Azone; $^{\triangle}P < 0.05$ *vs* Camphor

Component	Asymmetric stretch		Symmetric stretch	
	Higher shift/cm^{-1}	Wave number /cm^{-1}	Higher shift/cm^{-1}	Wave number /cm^{-1}
Control	0	2 920.66 ± 0.00	0	2 851.24 ± 0.01
Azone	1.90 ± 0.05	2 923.56 ± 0.05	0.96 ± 0.01	2 852.20 ± 0.01
Borneol	6.75 ± 0.55$^{*\triangle}$	2 927.41 ± 0.55	3.90 ± 0.38*	2 855.14 ± 0.38
Camphor	4.82 ± 0.26*	2 925.48 ± 0.26	2.89 ± 0.51*	2 854.13 ± 0.51

Table 2 Peak area of asymmetric and symmetric of C-H stretching absorption of porcine SC. Data were expressed as the $\bar{x} \pm$ SD, n = 3; $^{*}P < 0.05$ *vs* Azone; $^{\triangle}P < 0.05$ *vs* Camphor

Component	Asymmetric stretch		Symmetric stretch	
	Decrease /%	Area	Decrease /%	Area
Control	−	146.93 ± 4.23	−	372.91 ± 5.15
Azone	58.54 ± 2.63	60.91 ± 3.85	15.38 ± 1.17	315.56 ± 4.32
Borneol	76.81 ± 3.85$^{*\triangle}$	34.08 ± 5.67	55.55 ± 4.64$^{*\triangle}$	165.77 ± 9.87
Camphor	48.46 ± 5.00*	75.73 ± 7.35	29.89 ± 0.32*	261.46 ± 1.22

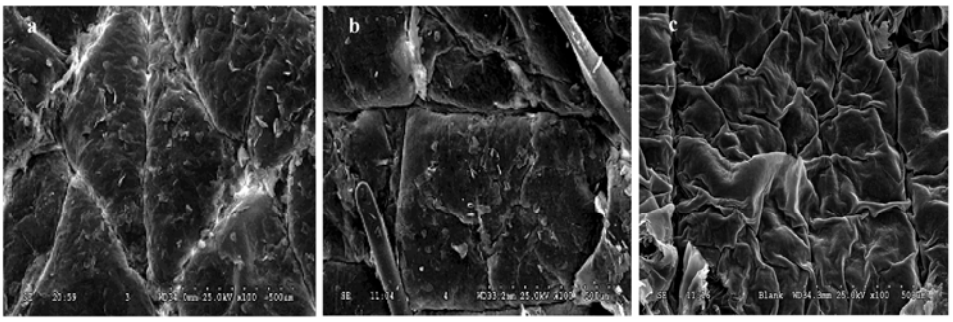


Figure 2 SEM images of SC treated with borneol (a), camphor (b) and blank control (c)

surface after the experiment. The skin areas treated with various enhancers were larger than that of control because of stretching skin wrinkles. It was possible that the larger skin area was one reason for the increased permeation flux of LGT.

SC is composed of corneocytes enclosed by a continuous intercellular lipids domain. Due to the enhancer solution, the intercellular lipid was probably dissolved and extracted by the solution, leading to the corneocytes separated from each other and desquamated from the intact SC. This is probably the reason why the scutella desquamate from the intact SC.

The desquamated degree of scutellum was estimated by an introduced apparent density (AD) of scutella. AD is expressed by the quantity of desquamated scutella in the unit area. Figure 3 showed that AD by borneol, camphor and Azone were 4.71, 1.55 and 0.78 pieces/mm^2. From Figure 2 and 3, the quantity of exfoliated scutella of borneol was much higher than that of camphor ($P < 0.05$). The SEM results demonstrated that the lipid extraction of borneol was stronger than that of camphor, which was consistent with the results of decreases in peak areas as measured by FT-IR. The results showed that a good correlation between increases in AD and decreases in peak area, and that SEM could be a new method to estimate the degree of extraction lipids.

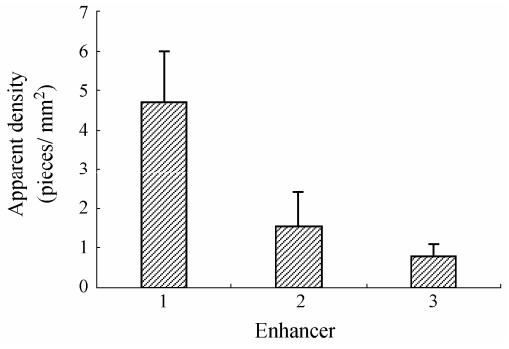


Figure 3 Apparent density (pieces/mm^2) of the exfoliated of SC flake treated with borneol (1), camphor (2) and Azone (3) ($n \geqslant 6$, $\bar{x} \pm$ SD)

3 *In vitro* permeation studies of LGT

The results of LGT permeated through the excised hairless porcine skin are listed in Table 3. Borneol and camphor showed statistically significant higher penetration compared to the control ($P < 0.05$). The percutaneous flux of LGT by borneol (7.28 μg·cm^{-2}·h^{-1}) was the highest, while the lag time of borneol (3.39 h) was the longest. It was interesting to note that the enhancer with the hydroxyl group (borneol) showed stronger enhancement activity than that with the ketone group (camphor), consistent with the previous report[28].

Table 3 Permeation parameters of enhancers through porcine skin to ligustrazine. Data were expressed as $\bar{x} \pm$ SD, $n = 3$; $^*P < 0.05$ *vs* Azone; $^\triangle P < 0.05$ *vs* Camphor

Enhancer	J_{ss} (μg·cm^{-2}·h^{-1})	T_L/h	$K_P \times 10^{-3}$/cm^{-2}·h^{-1}
Control	0.75 ± 0.28	3.31 ± 0.05*	23.63 ± 1.59
Azone	0.74 ± 0.09	1.86 ± 0.41	27.20 ± 4.47
Borneol	7.28 ± 0.50$^{*\triangle}$	3.39 ± 0.13$^{*\triangle}$	222.06 ± 7.08$^{*\triangle}$
Camphor	4.12 ± 0.16*	2.65 ± 0.99*	130.26 ± 5.26*

According to the results of microscopic FT-IR and macroscopic SEM, the penetration activity of borneol was stronger than that of camphor, consistent throughout the whole study. Structurally, borneol differs from camphor only by a hydroxy group at C2 instead of a ketone group. In SC, a large amount of ceramides were tightly embedded in the lipid bilayer through hydrogen bonding. This hydrogen bonding interaction made lipid bilayer strong and stable, and imparted the barrier trait to SC. The amide group of one ceramide was connected by hydrogen bond to the amide of another ceramide to form a network at the head of the ceramide. This tight network was disrupted by the enhancers possessing functional groups with hydrogen bond donors or accepters, thereby the permeation rate of the drug was improved [29]. The

molecular mechanism of the disruption was further explained as the preferential hydrogen bond of oxygen containing enhancers with ceramide head groups, thereby breaking the lateral/transverse hydrogen bond network of lipid bilayer[30]. The higher hydrogen bonding capability of the hydroxy group explains why the penetration activity of borneol is stronger than that of camphor.

Conclusion

The transdermal fluxes of LGT with borneol were stronger than those with camphor. The penetration activity of hydroxy group is stronger than that of ketone group. From the results of microscopic and the whole studies, the penetration mechanisms of borneol and camphor included disordering and extracting SC lipids.

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